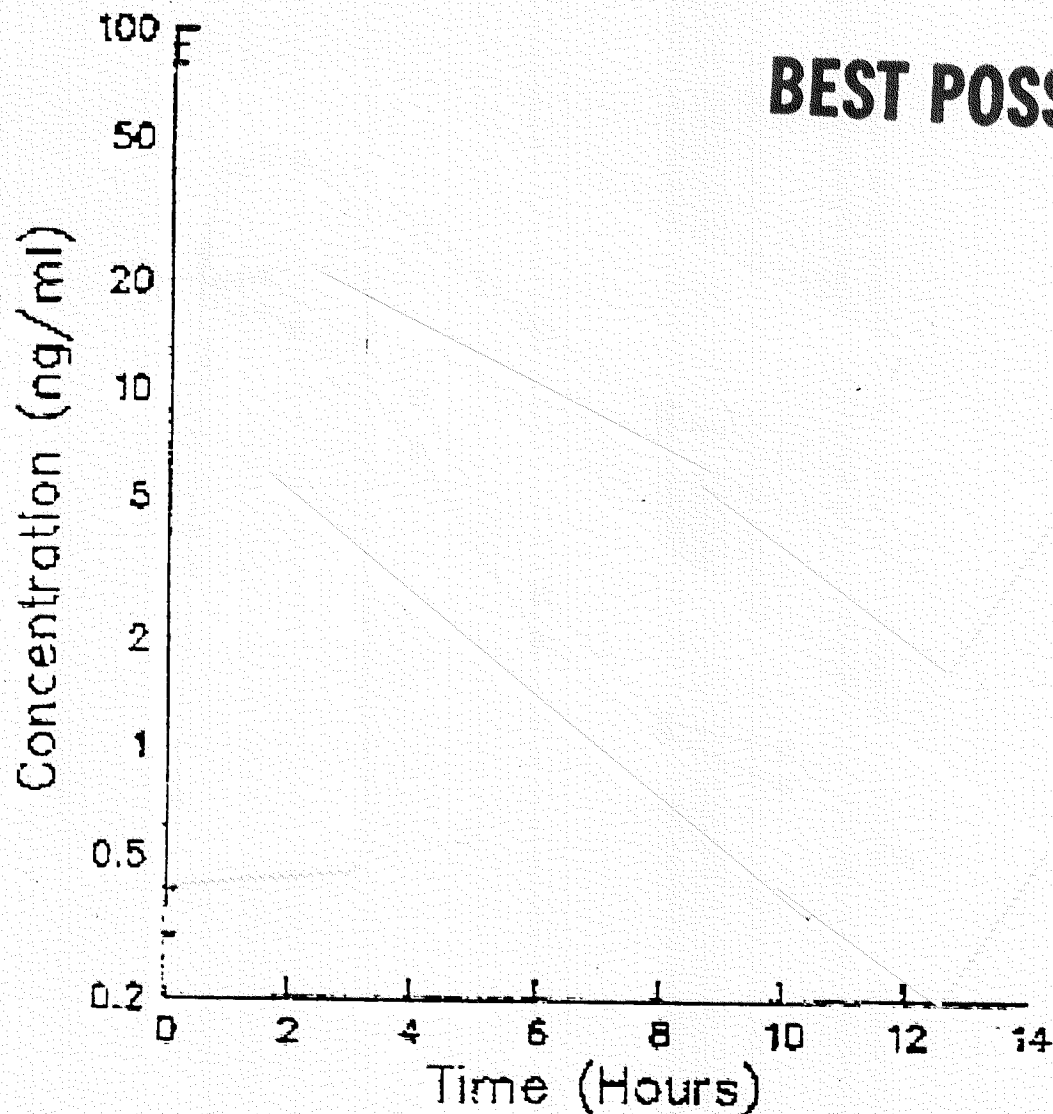


Figure 2

GR/91/062

Concentration of GR 68755 and Radioactive Material in Plasma Following Single Oral Administration of 1 mg GR 68755 (HCl salt) to Men at a Nominal Dose Level of 448 Base



Volunteer 1: GR 68755      Radioactive material

Volunteer 2: GR 68755      Radioactive material

Figure 4

Radiochromatogram of (a) Urine, Volunteer 1 (b) Urine, Volunteer 2 and (c) Feces, Volunteer 1. Following Single Oral Administration of  $^{14}\text{C}$ -EE 25733 (X2) (calcd to NMT at a Minimal Dose Level of 0.5 mg/kg)

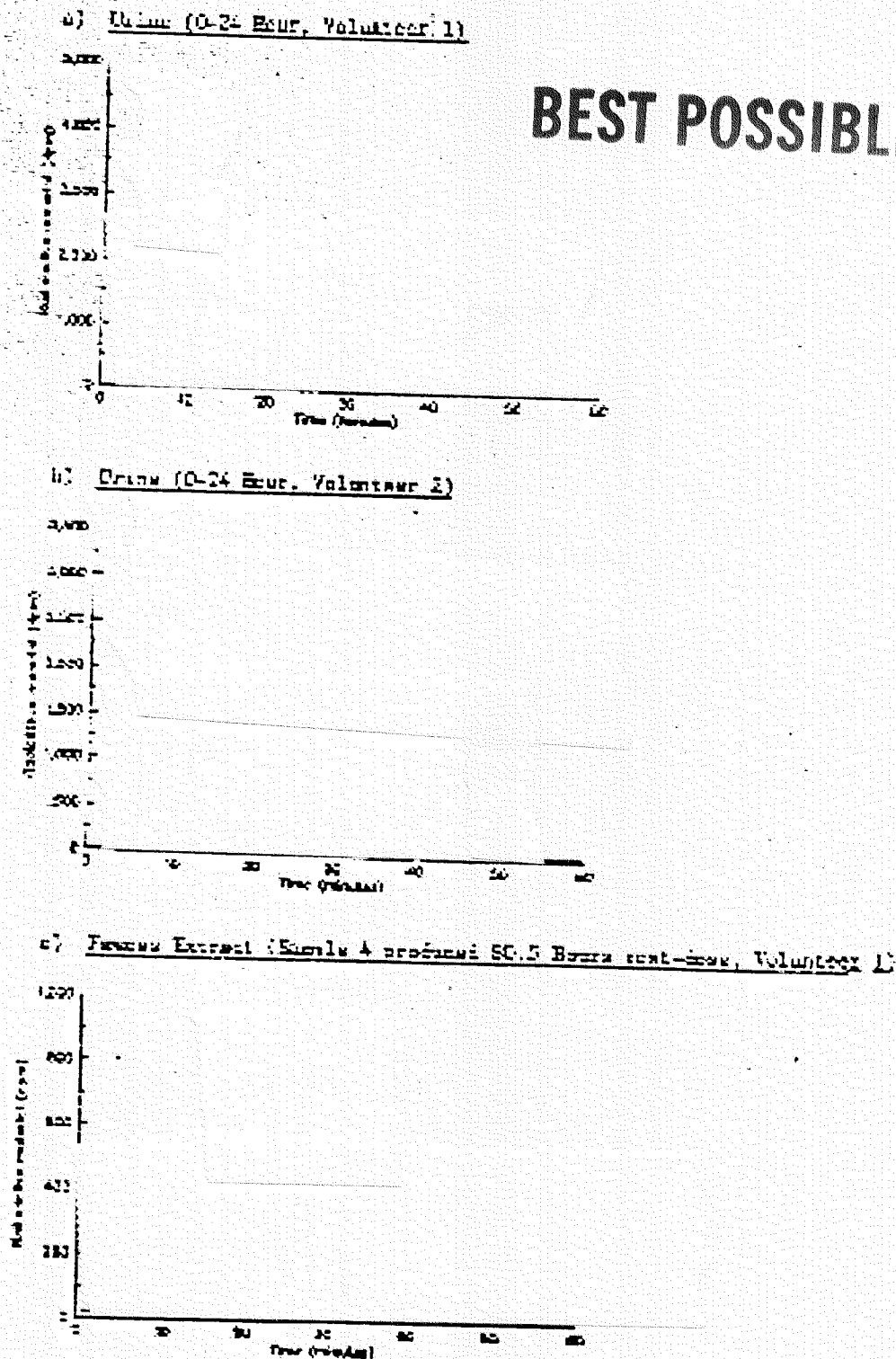
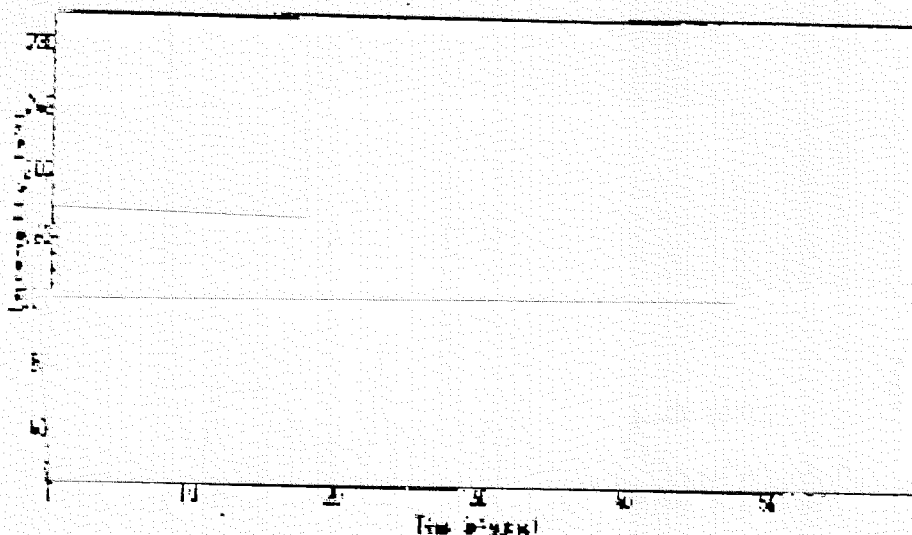


Figure 2

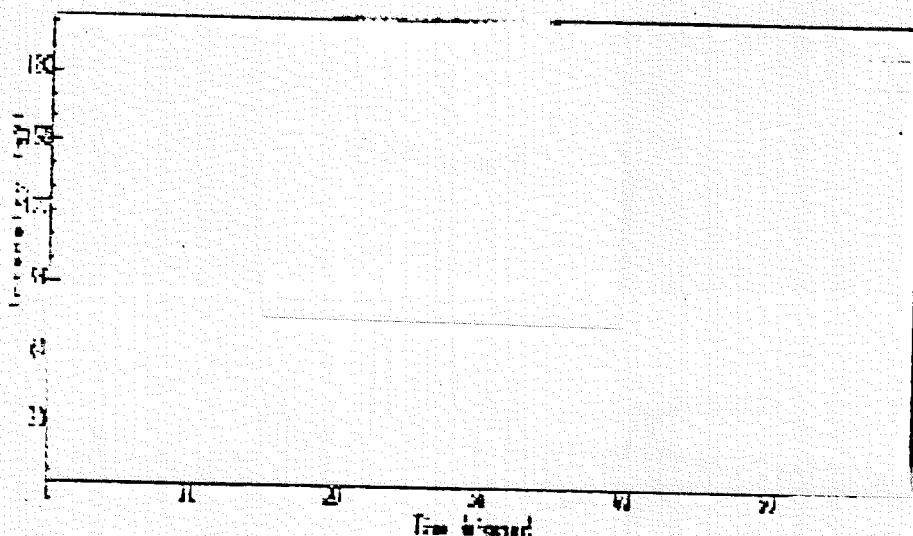
06/29/99

Radiochromatograms of (a) Urine and (b) Urine Treated with  $\beta$ -Glucuronidase. Following Single Oral Administration of 100-G2 68755 (HCl salt) to Man at a Normal Dose Level of 1 mg/kg.

a) Urine (0-24 Hour, Volume: 2) treated with buffer<sup>a</sup> (18 hours at 37°C)



b) Urine (0-24 Hour, Volume: 2) treated with  $\beta$ -Glucuronidase (18 hours at 37°C)



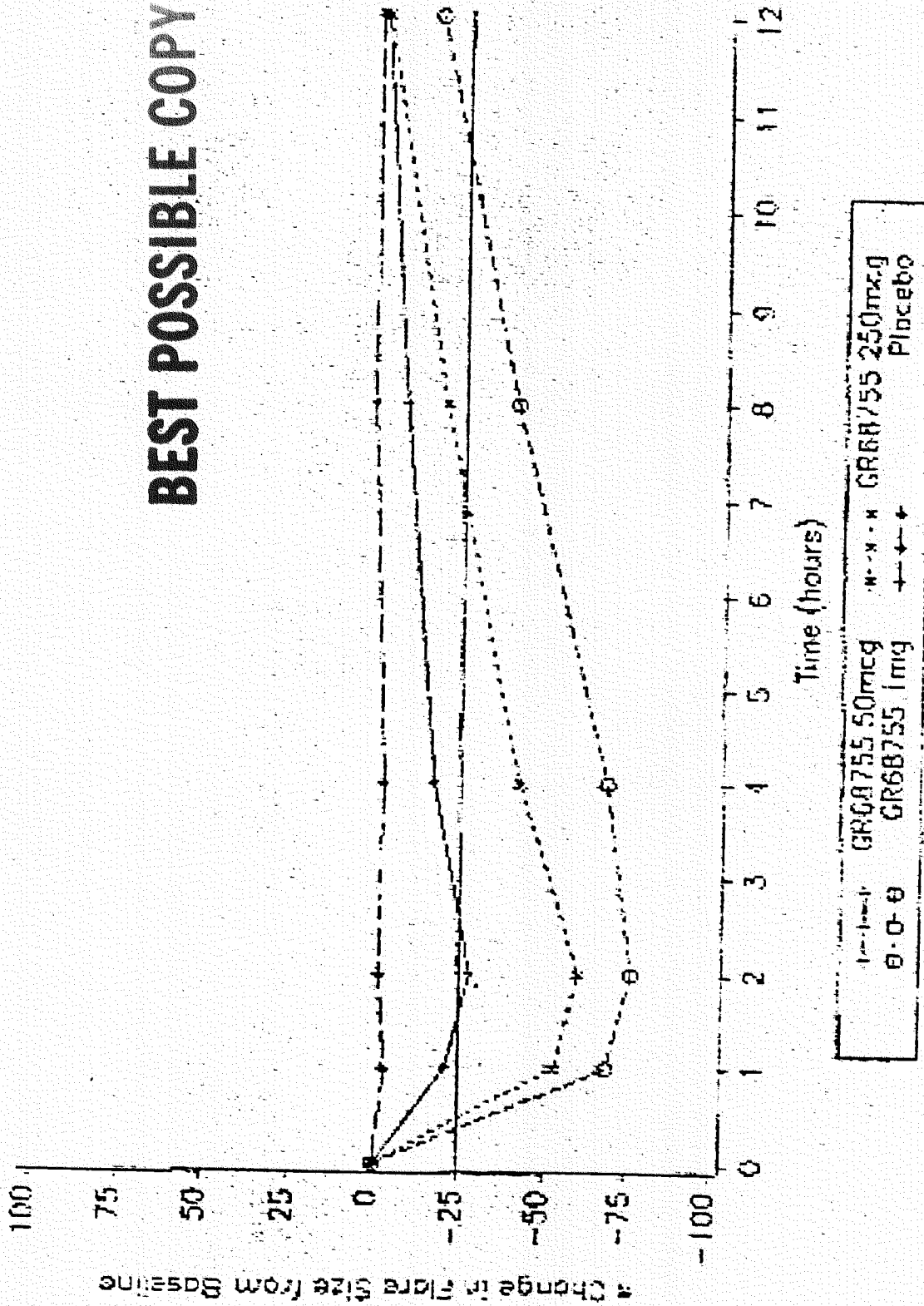
<sup>a</sup> 0.1M sodium acetate, pH 5.0

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## **APPENDIX 3      Extent and Duration of Suppression of Flare Response by Alosetron**

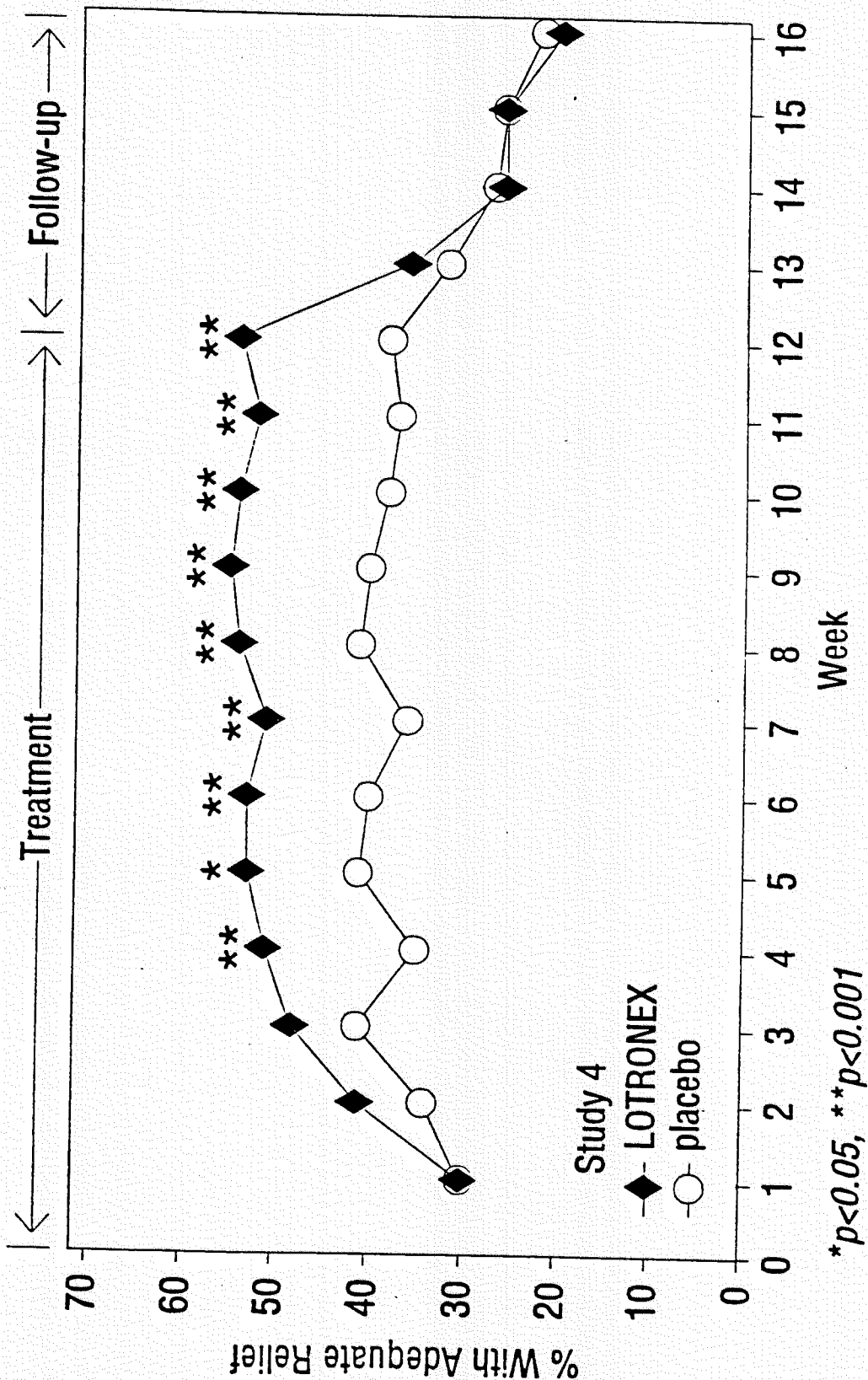
# Geometric Mean Percentage Change in 5-HT induced Flare Size

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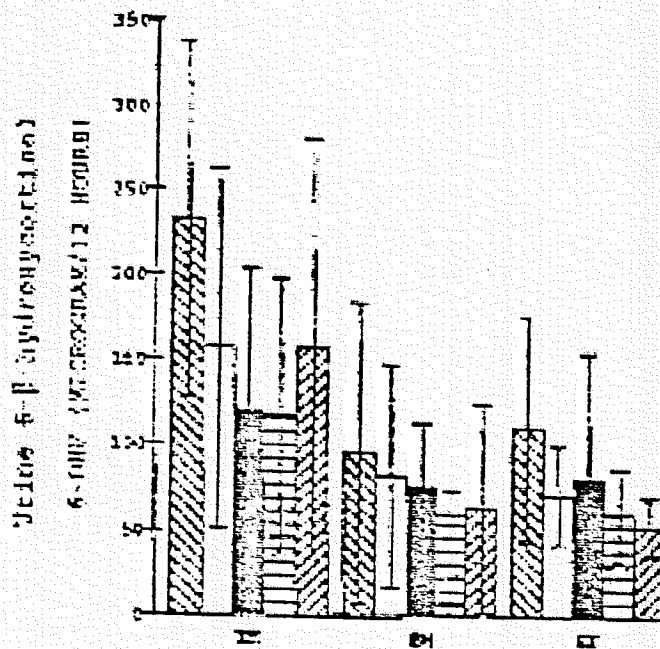
# Percentage of Female Patients Reporting Relief of IBS Pain and Discomfort in Study 4



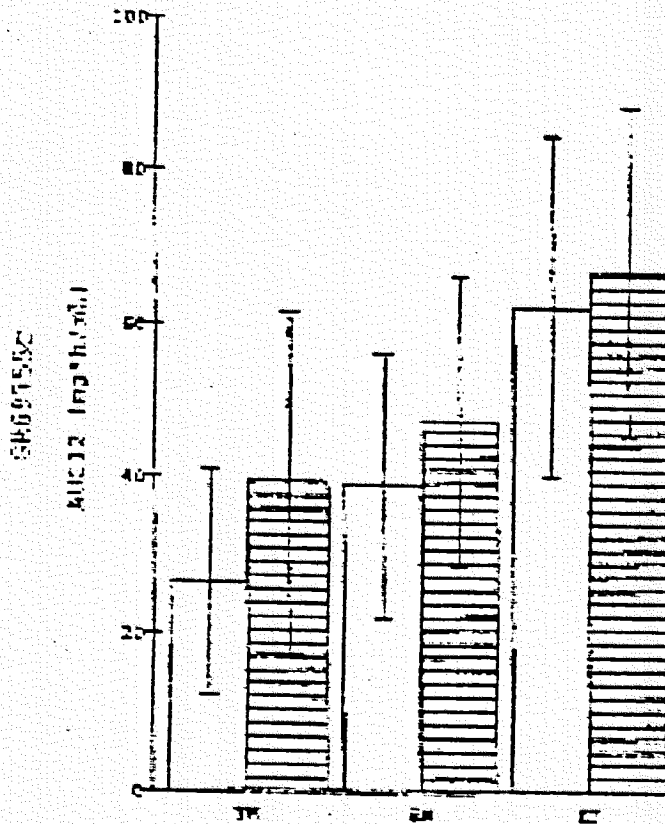
## APPENDIX 4      Cortisol Production, Urinary 6- $\beta$ - Hydroxycortisol Excretion, and Aloseton Exposure



Mean Amounts of 6- $\beta$ -hydroxycortisol in the Urine  
 and Mean AUC<sub>0-12</sub> Values of CR68755C



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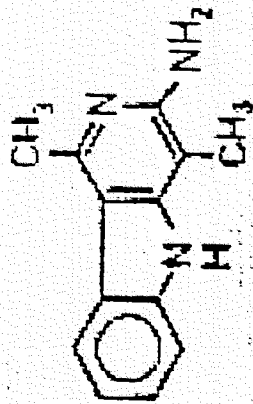


YM=Young Males  
 EM=Elderly Males  
 EF=Elderly Females

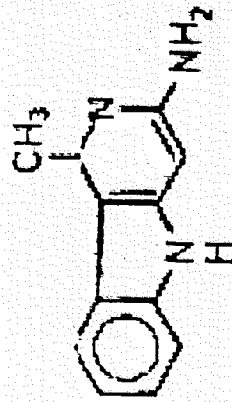
GROUP  
 DAY 2  
 DAY 29



## APPENDIX 5 Dietary Inducers of CYP1A2

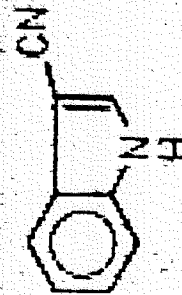


Trp-P-1

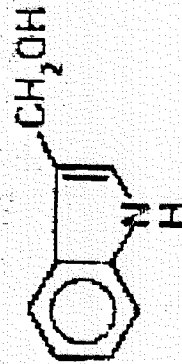


Trp-P-2

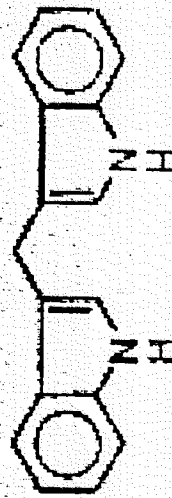
Tryptophan pyrolysis products found in fried or charcoal-broiled meat and fish.



Indole-3-acetonitrile



Indole-3-carbinol



3,3'-Diindolylmethane

Indoles found in cabbage and brussels sprouts.

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## **8.7. Summary of Benefits and Risks of Alosetron (GR68755) for the Treatment of Irritable Bowel Syndrome in Women**

### **8.7.1. Overview**

Irritable bowel syndrome (IBS) is characterized by chronic recurring abdominal pain, discomfort and alterations in bowel function. These changes in bowel function may manifest as diarrhea, constipation, or alternating diarrhea and constipation. Irritable bowel syndrome (IBS) is estimated to affect 15-20% of the population with females representing 70-75% of sufferers.

The efficacy and safety of alosetron has been evaluated in 3,670 patients and healthy volunteers enrolled in 52 completed studies worldwide, including 1810 patients with IBS who have received alosetron monotherapy. The clinical studies summarized in the Integrated Summary of Efficacy and the Integrated Summary of Safety contained in this application reveal alosetron, a 5-HT<sub>3</sub> receptor antagonist, to be efficacious and well tolerated in the treatment of females with diarrhea predominant IBS.

### **8.7.2. Efficacy of Alosetron in IBS**

Two adequate and well-controlled Phase III trials conclusively demonstrated the effectiveness of alosetron as a novel pharmacological treatment for a significant proportion of IBS patients. Alosetron provided significant improvements in the relief of abdominal pain and discomfort within one to four weeks of treatment initiation in females with diarrhea-predominant IBS. Beneficial effects persisted throughout treatment with no evidence of tolerance with continued therapy. Symptoms returned rapidly upon stopping therapy, although no exacerbation was observed. The prospectively defined primary endpoint of both studies was "adequate relief of IBS pain and discomfort" which represents a scientifically-validated, patient-assessed endpoint derived in collaboration with a panel of IBS experts. The adequate relief endpoint significantly correlates with improvements in pain severity, pain-free days, urgency, stool frequency and consistency.

Females with diarrhea-predominant IBS also exhibited significant improvements in urgency, bowel frequency, and stool consistency by the end of the first week of alosetron treatment. Again, improvements persisted throughout treatment. Tolerance did not develop with continued treatment and improvements decreased rapidly upon stopping therapy.

Surveys of non-constipated females with IBS have identified the three most bothersome symptoms to be abdominal pain and discomfort, urgency, and stool frequency. As clearly demonstrated in these replicate studies, alosetron treatment significantly improved all three of these parameters in females with diarrhea-predominant IBS. These data provide compelling proof of the benefit of chronic alosetron treatment for the most important symptoms suffered by females with diarrhea-predominant IBS.

### 8.7.3. Safety of Alosetron

#### 8.7.3.1. Clinical

The extensive non-clinical and clinical database with alosetron confirms an excellent safety profile across all populations studied. The cumulative clinical exposure has been derived from 3670 volunteers and patients, participating in 52 completed studies. In the phase II and III programs 1263 IBS patients (1079 women and 184 men) received twice daily dosing of alosetron for up to 12 weeks. In the long-term safety study, 330 patients (226 women and 104 men) have received 1mg BID alosetron for at least 6 months duration (study ongoing for 12 months of chronic therapy).

In the phase II and III studies, constipation was the only adverse event occurring at substantially higher frequency in alosetron-treated patients, in comparison to those receiving placebo. In the 12-week repeat dose studies of 1mg BID alosetron, constipation occurred in 27% of patients (n=702) as compared to 5% on placebo. In the long-term safety study constipation was reported as an adverse event in 31% of subjects taking 1mg BID alosetron; therefore, a similar incidence of constipation was evident for both three and six month alosetron therapy. If constipation occurred, it tended to do so within the first month of therapy and, in the majority of cases, was transient. Of patients reporting constipation, approximately one-third of these constipated patients withdrew from the studies secondary to constipation. As part of the study design, patients were not permitted routine laxative use. Among patients with diarrhea-predominant IBS who completed the studies, the weekly adequate relief rates were comparable between constipated and non-constipated subjects. Therefore, the majority of subjects reporting constipation continue to derive clinical benefit from alosetron therapy. No other adverse event, serious adverse event, or laboratory values were noteworthy during the alosetron clinical development program.

*In vitro* and *in vivo* drug interaction studies indicate little potential for significant drug interactions by alosetron. Since alosetron is metabolized by a variety of hepatic enzymes, alosetron metabolism is unlikely to be significantly affected by inhibition or induction of any one enzyme. Alosetron does not appear to induce hepatic cytochromes P450. Specific alosetron interaction studies conducted with cisapride, theophylline and oral contraceptives revealed no evidence of interaction. Assessment of electrocardiographic changes during alosetron treatment and concomitantly with cisapride also revealed no significant effects.

#### 8.7.3.2. Non-Clinical Findings and Relevance to Clinical Studies

Mutagenicity and carcinogenicity studies in mice and rats *in vivo* and *in vitro* revealed no evidence of genotoxicity or neoplasia following 2 year exposure to alosetron. Throughout the clinical development program, no increased incidence of treatment-related neoplasia was observed.

In some animal studies, a reversible diminution in hearing acuity was observed in a minority of RH rats and beagle dogs after 12 month oral administration of high dose (~1000-fold the recommended dose) alosetron. However, changes rapidly reversed



within one month of cessation of alosetron treatment. No effect on hearing was noted after 102 week administration of alosetron to Wistar rats. In clinical studies, no increase in hearing-related adverse events have been noted during alosetron treatment. In the 12 month long-term safety study, audiograms are being performed at baseline and after 6 and 12 months of treatment. The results of the audiograms will be available in the 120 day safety update to this application.

Studies in rats and rabbits revealed no significant adverse effects of high dose alosetron on reproductive function, fertility, or embryofetal toxicity. Minimal clinical information is available on the use of alosetron in pregnancy in IBS patients.

To date, the non-clinical and clinical experience reveals an extremely favorable safety profile for alosetron with constipation, a class effect of 5-HT<sub>3</sub> receptor antagonists, the only notable adverse event observed.

#### **8.7.4. Unmet Need**

IBS is a female predominant disease with 70-75% of sufferers being women. In two Phase III studies enrolling non-constipated female IBS patients, approximately 70% of patients were classified by their physician as having diarrhea-predominant IBS. World-wide there is no "gold standard" treatment for IBS. In non-constipated female IBS patients, no agent has been shown to be of proven benefit in the treatment of the patient's most bothersome symptoms of abdominal pain, urgency and increased stool frequency. In the pivotal Phase III studies, alosetron, by contrast, produced significant improvement in all of these most bothersome symptoms in diarrhea-predominant patients.

Although a few agents in the United States are labeled for the treatment of IBS or symptoms of IBS, most are described as "adjunctive" treatment. Additionally, some have the qualifier that they are "possibly" effective; reflecting the market introduction of these products prior to establishment of the current regulatory standards for providing substantial evidence of effectiveness. Little published clinical data exists for these products. In contrast to data presented for alosetron, no product commercially available in the United States has been proven effective for treatment of IBS in two large, multicenter trials. Since products with a labeled claim for IBS contain an anticholinergic agent as one of the primary active ingredients, numerous adverse events are associated with their use including: constipation, bloating, abdominal pain, and numerous CNS-related events. Further, these agents should not be used for conditions where anticholinergics are contraindicated.

By contrast to available agents, the efficacy of alosetron has been confirmed in two large, identically-designed, and contemporaneously conducted Phase III trials. In these two pivotal studies, alosetron provided consistent benefit in diarrhea-predominant female IBS patients for the most bothersome symptoms of IBS: pain, urgency to defecate and frequency of stooling. As a single agent, alosetron consistently improved all of these symptoms throughout the treatment period. Upon discontinuation of therapy, symptoms rapidly returned. This compelling efficacy, combined with a very favorable safety profile, provide persuasive evidence for alosetron as a therapeutic advance for female patients with diarrhea-predominant IBS.

#### 8.7.5. Future Recommended Studies

#### 8.7.6. Summary

In comparison to existing therapies, alosetron represents a significant improvement for the treatment of females with diarrhea-predominant IBS. Alosetron provides robust efficacy in relieving the most bothersome IBS symptoms: pain, urgency to defecate, and frequency of stooling. The compelling evidence of effectiveness combined with a very favorable safety profile provides persuasive evidence for alosetron as a therapeutic advance and a first-line monotherapy for the significant population of females with diarrhea-predominant IBS patients.

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